

What is claimed is:

1. A method for degrading a transcription factor of a glucose metabolism-related gene, wherein the method comprises making calpain coexist with the transcription factor of the glucose metabolism-related gene in the presence of calcium.
2. A method for degrading a transcription factor of a glucose metabolism-related gene, wherein the method comprises changing the degree of the degradation of the transcription factor of the glucose metabolism-related gene by calcium concentration.
3. A method for degrading a transcription factor of a glucose metabolism-related gene, wherein the method comprises making m-calpain and/or  $\mu$ -calpain coexist with the transcription factor of the glucose metabolism-related gene in the presence of calcium.
4. The degradation method according to any one of claims 1 to 3, wherein the transcription factor of the glucose metabolism-related gene is at least one member selected from the group consisting of hepatocyte nuclear factor 4 $\alpha$ , hepatocyte nuclear factor 1 $\alpha$  and insulin promoter factor 1.
5. A method for degrading hepatocyte nuclear factor 4 $\alpha$  (HNF-4 $\alpha$ ), wherein the method comprises making m-calpain and/or  $\mu$ -calpain coexist with HNF-4 $\alpha$  in the presence of calcium.
6. A method for degrading hepatocyte nuclear factor 1 $\alpha$  (HNF-1 $\alpha$ ), wherein the method comprises making m-calpain and/or  $\mu$ -calpain coexist with HNF-1 $\alpha$  in the presence of calcium.
7. A method for degrading insulin promoter factor 1 (IPF-1), wherein the method comprises making m-calpain and/or  $\mu$ -calpain coexist with IPF-1 in the presence of calcium.
8. A method for inhibiting the degradation of a transcription factor of a glucose metabolism-related gene, wherein the method comprises inhibiting calpain activity.
9. A method for inhibiting the degradation of a transcription factor of a glucose metabolism-related gene, wherein the method comprises inhibiting the cleavage by calpain of the transcription factor of the glucose metabolism-related gene.
10. A method for inhibiting the degradation of a transcription factor of a glucose metabolism-related gene, wherein the method comprises inhibiting the binding of calpain to the transcription factor of the glucose metabolism-related gene.

11. A method for inhibiting the degradation of a transcription factor of a glucose metabolism-related gene, wherein the method comprises treating an *in vitro* sample containing at least calpain and the transcription factor of the glucose metabolism-related gene with a substance that inhibits calpain activity.
12. A method for inhibiting the degradation of a transcription factor of a glucose metabolism-related gene, wherein the method comprises treating a cell expressing at least calpain and the transcription factor of the glucose metabolism-related gene with a substance that inhibits calpain activity.
13. The method for inhibiting the degradation of a transcription factor of a glucose metabolism-related gene according to claim 12, wherein the cell is a cell that is carried by a mammal.
14. The method for inhibiting the degradation of a transcription factor of a glucose metabolism-related gene according to claim 13, wherein the cell that is carried by a mammal is a pancreatic  $\beta$  cell.
15. The method for inhibiting the degradation of a transcription factor of a glucose metabolism-related gene according to any one of claims 11 to 14, wherein the substance that inhibits calpain activity is one or more substances selected from the group consisting of an antibody that recognizes calpain, an antibody that recognizes the transcription factor of the glucose metabolism-related gene, and a calpain inhibitor.
16. The method for inhibiting the degradation of a transcription factor of a glucose metabolism-related gene according to claim 15, wherein the calpain inhibitor is N-Acetyl-Leu-Leu-Met-CHO, N-Acetyl-Leu-Leu-Nle-CHO, Z-Leu-Leu-Tyr-CH<sub>2</sub>F, Mu-Val-HPh-CH<sub>2</sub>F, 4-fluorophenylsulfonyl-Val-Leu-CHO, Leu-Leu-Phe-CH<sub>2</sub>Cl or Z-Val-Phe-CHO.
17. The method for inhibiting the degradation of a transcription factor of a glucose metabolism-related gene according to any one of claims 11 to 14, wherein the substance that inhibits calpain activity is a peptide containing at least one amino acid sequence of a

calpain-recognized cleavage site in the transcription factor of the glucose metabolism-related gene.

18. The method for inhibiting the degradation of a transcription factor of a glucose metabolism-related gene according to any one of claims 11 to 14, wherein the substance that inhibits calpain activity is a peptide that comprises three or more consecutive amino acid residues from the amino acid sequence set forth in any of SEQ ID NOS: 1 to 3 in the sequence listing and contains at least one amino acid sequence of a calpain-recognized cleavage site in the transcription factor of the glucose metabolism-related gene.

19. The method for inhibiting the degradation of a transcription factor of a glucose metabolism-related gene according to claim 18, wherein the calpain-recognized cleavage site in the transcription factor of the glucose metabolism-related gene is selected from the group consisting of Leu-Tyr, Leu-Met, Leu-Arg, Val-Tyr, Val-Met and Val-Arg.

20. The method for inhibiting the degradation of a transcription factor of a glucose metabolism-related gene according to any one of claims 8 to 19, wherein calpain is m-calpain and/or  $\mu$ -calpain.

21. The method for inhibiting the degradation of a transcription factor of a glucose metabolism-related gene according to any one of claims 8 to 20, wherein the transcription factor of the glucose metabolism-related gene is at least one member selected from the group consisting of hepatocyte nuclear factor 4 $\alpha$ , hepatocyte nuclear factor 1 $\alpha$  and insulin promoter factor 1.

22. A method for inhibiting the degradation of hepatocyte nuclear factor 4 $\alpha$ , wherein the method comprises inhibiting the activity of m-calpain and/or  $\mu$ -calpain.

23. A method for inhibiting the degradation of hepatocyte nuclear factor 1 $\alpha$ , wherein the method comprises inhibiting the activity of m-calpain and/or  $\mu$ -calpain.

24. A method for inhibiting the degradation of insulin promoter factor 1, wherein the method comprises inhibiting the activity of m-calpain and/or  $\mu$ -calpain.

25. An agent for degrading a transcription factor of a glucose metabolism-related gene, wherein the agent contains an effective dose of calpain as an active ingredient.

26. The agent for degrading a transcription factor of a glucose metabolism-related gene according to claim 25, wherein calpain is m-calpain and/or  $\mu$ -calpain.
27. The agent for degrading a transcription factor of a glucose metabolism-related gene according to claim 25 or 26, wherein the transcription factor of the glucose metabolism-related gene is at least one member selected from the group consisting of hepatocyte nuclear factor 4 $\alpha$ , hepatocyte nuclear factor 1 $\alpha$  and insulin promoter factor 1.
28. An agent for degrading hepatocyte nuclear factor 4 $\alpha$ , wherein the agent contains an effective dose of m-calpain and/or  $\mu$ -calpain as an active ingredient.
29. An agent for degrading hepatocyte nuclear factor 1 $\alpha$ , wherein the agent contains an effective dose of m-calpain and/or  $\mu$ -calpain as an active ingredient.
30. An agent for degrading insulin promoter factor 1, wherein the agent contains an effective dose of m-calpain and/or  $\mu$ -calpain as an active ingredient.
31. An agent for inhibiting the degradation of a transcription factor of a glucose metabolism-related gene, wherein the agent inhibits calpain activity.
32. An agent for inhibiting the degradation of a transcription factor of a glucose metabolism-related gene, wherein the agent inhibits the cleavage of the transcription factor of the glucose metabolism-related gene by calpain.
33. An agent for inhibiting the degradation of a transcription factor of a glucose metabolism-related gene, wherein the agent inhibits the binding of calpain to the transcription factor of the glucose metabolism-related gene.
34. An agent for inhibiting the degradation of a transcription factor of a glucose metabolism-related gene, which contains an effective dose of a substance that inhibits calpain activity as an active ingredient.
35. The agent for inhibiting the degradation of a transcription factor of a glucose metabolism-related gene according to claim 34, wherein the substance that inhibits calpain activity is one or more substances selected from the group consisting of an antibody that recognizes calpain, an antibody that recognizes the transcription factor of the glucose

metabolism-related gene, and a calpain inhibitor.

36. The agent for inhibiting the degradation of a transcription factor of a glucose metabolism-related gene according to claim 35, wherein the calpain inhibitor is N-Acetyl-Leu-Leu-Met-CHO, N-Acetyl-Leu-Leu-Nle-CHO, Z-Leu-Leu-Tyr-CH<sub>2</sub>F, Mu-Val-HPh-CH<sub>2</sub>F, 4-fluorophenylsulfonyl-Val-Leu-CHO, Leu-Leu-Phe-CH<sub>2</sub>Cl or Z-Val-Phe-CHO.

37. The agent for inhibiting the degradation of a transcription factor of a glucose metabolism-related gene according to claim 34, wherein the substance that inhibits calpain activity is a peptide containing at least one amino acid sequence of a calpain-recognized cleavage site in the transcription factor of the glucose metabolism-related gene.

38. The agent for inhibiting the degradation of a transcription factor of a glucose metabolism-related gene according to claim 34, wherein the substance that inhibits calpain activity is a peptide that comprises three or more consecutive amino acid residues from the amino acid sequence set forth in any of SEQ ID NOS: 1 to 3 in the sequence listing and contains at least one amino acid sequence of a calpain-recognized cleavage site in the transcription factor of the glucose metabolism-related gene.

39. The agent for inhibiting the degradation of a transcription factor of a glucose metabolism-related gene according to claim 38, wherein the calpain-recognized cleavage site in the transcription factor of the glucose metabolism-related gene is selected from the group consisting of Leu-Tyr, Leu-Met, Leu-Arg, Val-Tyr, Val-Met and Val-Arg.

40. The agent for inhibiting the degradation of a transcription factor of a glucose metabolism-related gene according to any one of claims 31 to 39, wherein calpain is m-calpain and/or  $\mu$ -calpain.

41. The agent for inhibiting the degradation of a transcription factor of a glucose metabolism-related gene according to any one of claims 31 to 40, wherein the transcription factor of the glucose metabolism-related gene is at least one member selected from the group consisting of hepatocyte nuclear factor 4 $\alpha$ , hepatocyte nuclear factor 1 $\alpha$ , and insulin promoter

factor 1.

42. An agent for inhibiting the degradation of hepatocyte nuclear factor 4 $\alpha$ , wherein the agent inhibits the activity of m-calpain and/or  $\mu$ -calpain.

43. An agent for inhibiting the degradation of hepatocyte nuclear factor 1 $\alpha$ , wherein the agent inhibits the activity of m-calpain and/or  $\mu$ -calpain.

44. An agent for inhibiting the degradation of insulin promoter factor 1, wherein the agent inhibits the activity of m-calpain and/or  $\mu$ -calpain.

45. A method for inhibiting production of a gene product of a glucose metabolism-related gene, wherein the method comprises degrading a transcription factor of the glucose metabolism-related gene by using calpain.

46. The method for inhibiting production of a gene product of a glucose metabolism-related gene according to claim 45, wherein calpain is m-calpain and/or  $\mu$ -calpain.

47. A method for inhibiting production of a gene product of a glucose metabolism-related gene, wherein the method comprises degrading at least one transcription factor selected from the group consisting of hepatocyte nuclear factor 4 $\alpha$ , hepatocyte nuclear factor 1 $\alpha$ , and insulin promoter factor 1 by using m-calpain and/or  $\mu$ -calpain.

48. The method for inhibiting production of a gene product of a glucose metabolism-related gene according to any one of claims 45 to 47, wherein the glucose metabolism-related gene is the insulin gene or glucose transporter 2 gene.

49. A method for enhancing production of a gene product of a glucose metabolism-related gene, wherein the method comprises inhibiting the degradation of a transcription factor of the glucose metabolism-related gene caused by calpain.

50. The method for enhancing production of a gene product of a glucose metabolism-related gene according to claim 49, wherein calpain is m-calpain and/or  $\mu$ -calpain.

51. A method for enhancing production of a gene product of a glucose metabolism-related gene, wherein the method comprises inhibiting the degradation caused by m-calpain and/or  $\mu$ -calpain of at least one member selected from the group consisting of hepatocyte nuclear factor 4 $\alpha$ ,

hepatocyte nuclear factor 1 $\alpha$  and insulin promoter factor 1.

52. The method for enhancing production of a gene product of a glucose metabolism-related gene according to any one of claims 49 to 51, wherein the glucose metabolism-related gene is insulin gene or glucose transporter 2 gene.

53. A method for regulating production of a gene product of a glucose metabolism-related gene, wherein the method comprises changing the degree of degradation of a glucose metabolism-related gene by calcium concentration.

54. A method for regulating production of a gene product of a glucose metabolism-related gene, wherein the method comprises changing the degree of degradation of at least one member selected from the group consisting of hepatocyte nuclear factor 4 $\alpha$ , hepatocyte nuclear factor 1 $\alpha$  and insulin promoter factor 1 by calcium concentration.

55. A method for enhancing production of a gene product of a glucose metabolism-related gene, wherein the method comprises using the method for inhibiting the degradation of a transcription factor according to any one of claims 8 to 24.

56. A method for enhancing production of a gene product of a gene on which at least one member selected from the group consisting of hepatocyte nuclear factor 4 $\alpha$ , hepatocyte nuclear factor 1 $\alpha$  and insulin promoter factor 1 acts as a transcription factor, wherein the method comprises using the method for inhibiting the degradation of a transcription factor according to any one of claims 8 to 24.

57. A method for enhancing production of a gene product of the insulin gene and/or glucose transporter 2 gene, wherein the method comprises using the method for inhibiting the degradation of a transcription factor according to any one of claims 8 to 24.

58. A method for preventing and/or treating a disease attributable to the degradation of a transcription factor of a glucose metabolism-related gene, wherein the method comprises using the method for inhibiting the degradation of a transcription factor according to any one of claims 8 to 24.

59. A method for preventing and/or treating a disease attributable to the degradation of at least one member selected from the group consisting of hepatocyte nuclear factor 4 $\alpha$ , hepatocyte nuclear factor 1 $\alpha$  and insulin promoter factor 1, wherein the method comprises using the method for inhibiting the degradation of a transcription factor according to any one of claims 8 to 24.
60. A method for preventing and/or treating a disease attributable to a decrease in a gene product of a glucose metabolism-related gene, wherein the method comprises using the method for inhibiting the degradation of a transcription factor according to any one of claims 8 to 24.
61. A method for preventing and/or treating a disease attributable to a decrease in a gene product of a gene on which at least one member selected from the group consisting of hepatocyte nuclear factor 4 $\alpha$ , hepatocyte nuclear factor 1 $\alpha$  and insulin promoter factor 1 acts as a transcription factor, wherein the method comprises using the method for inhibiting the degradation of a transcription factor according to any one of claims 8 to 24.
62. A method for preventing and/or treating a disease attributable to a decrease in a gene product of the insulin gene and/or glucose transporter 2 gene, wherein the method comprises using the method for inhibiting the degradation of a transcription factor according to any one of claims 8 to 24.
63. A method for preventing and/or treating diabetes, wherein the method comprises using the method for inhibiting the degradation of a transcription factor according to any one of claims 8 to 24.
64. A method for enhancing production of a gene product of a glucose metabolism-related gene, wherein the method comprises using the agent for inhibiting the degradation of a transcription factor according to any one of claims 31 to 44.
65. A method for enhancing production of a gene product of a gene on which at least one member selected from the group consisting of hepatocyte nuclear factor 4 $\alpha$ , hepatocyte nuclear factor 1 $\alpha$  and insulin promoter factor 1 acts as a transcription factor, wherein the method comprises using the agent for inhibiting the degradation of a transcription factor according to any



one of claims 31 to 44.

66. A method for enhancing production of a gene product of the insulin gene and/or glucose transporter 2 gene, wherein the method comprises using the agent for inhibiting the degradation of a transcription factor according to any one of claims 31 to 44.

67. A method for preventing and/or treating a disease attributable to the degradation of a transcription factor of a glucose metabolism-related gene, wherein the method comprises using the agent for inhibiting the degradation of a transcription factor according to any one of claims 31 to 44.

68. A method for preventing and/or treating a disease attributable to the degradation of at least one member selected from the group consisting of hepatocyte nuclear factor 4 $\alpha$ , hepatocyte nuclear factor 1 $\alpha$  and insulin promoter factor 1, wherein the method comprises using the agent for inhibiting the degradation of a transcription factor according to any one of claims 31 to 44.

69. A method for preventing and/or treating a disease attributable to a decrease in a gene product of a glucose metabolism-related gene, wherein the method comprises using the agent for inhibiting the degradation of a transcription factor according to any one of claims 31 to 44.

70. A method for preventing and/or treating a disease attributable to a decrease in a gene product of a gene on which at least one member selected from the group consisting of hepatocyte nuclear factor 4 $\alpha$ , hepatocyte nuclear factor 1 $\alpha$  and insulin promoter factor 1 acts as a transcription factor, wherein the method comprises using the agent for inhibiting the degradation of a transcription factor according to any one of claims 31 to 44.

71. A method for preventing and/or treating a disease attributable to a decrease in a gene product of the insulin gene and/or glucose transporter 2 gene, wherein the method comprises using the agent for inhibiting the degradation of a transcription factor according to any one of claims 31 to 44.

72. A method for preventing and/or treating diabetes, wherein the method comprises using the agent for inhibiting the degradation of a transcription factor according to any one of claims 31 to 44.

73. An agent for enhancing production of a gene product of a glucose metabolism-related gene, wherein the agent contains an effective dose of the agent for inhibiting the degradation of a transcription factor according to any one of claims 31 to 44.
74. An agent for enhancing production of a gene product of a gene on which at least one member selected from the group consisting of hepatocyte nuclear factor 4 $\alpha$ , hepatocyte nuclear factor 1 $\alpha$  and insulin promoter factor 1 acts as a transcription factor, wherein the agent contains an effective dose of the agent for inhibiting the degradation of a transcription factor according to any one of claims 31 to 44.
75. An agent for enhancing production of a gene product of the insulin gene and/or glucose transporter 2 gene, wherein the agent contains an effective dose of the agent for inhibiting the degradation of a transcription factor according to any one of claims 31 to 44.
76. A pharmaceutical composition which contains an effective dose of the agent for inhibiting the degradation of a transcription factor according to any one of claims 31 to 44.
77. An agent for preventing and/or treating a disease attributable to the degradation of a transcription factor of a glucose metabolism-related gene, wherein the agent contains an effective dose of the agent for inhibiting the degradation of a transcription factor according to any one of claims 31 to 44.
78. An agent for preventing and/or treating a disease attributable to the degradation of at least one member selected from the group consisting of hepatocyte nuclear factor 4 $\alpha$ , hepatocyte nuclear factor 1 $\alpha$  and insulin promoter factor 1, wherein the agent contains an effective dose of the agent for inhibiting the degradation of a transcription factor according to any one of claims 31 to 44.
79. An agent for preventing and/or treating a disease attributable to a decrease in a gene product of a glucose metabolism-related gene, wherein the agent contains an effective dose of the agent for inhibiting the degradation of a transcription factor according to any one of claims 31 to 44.
80. An agent for preventing and/or treating a disease attributable to a decrease in a gene product of a gene on which at least one member selected from the group consisting of hepatocyte nuclear

factor 4 $\alpha$ , hepatocyte nuclear factor 1 $\alpha$  and insulin promoter factor 1 acts as a transcription factor, wherein the agent contains an effective dose of the agent for inhibiting the degradation of a transcription factor according to any one of claims 31 to 44.

81. An agent for preventing and/or treating a disease attributable to a decrease in a gene product of insulin gene and/or glucose transporter 2 gene, wherein the agent contains an effective dose of the agent for inhibiting the degradation of a transcription factor according to any one of claims 31 to 44.

82. An agent for preventing and/or treating diabetes, wherein the agent contains an effective dose of the agent for inhibiting the degradation of a transcription factor according to any one of claims 31 to 44.

83. A method for preventing and/or treating liver adenoma or hepatocellular carcinoma, wherein the method comprises using the degradation inhibition method according to claim 23.

84. A method for preventing and/or treating liver adenoma or hepatocellular carcinoma, wherein the method comprises using the degradation inhibitory agent according to claim 43.

85. An agent for preventing and/or treating liver adenoma or hepatocellular carcinoma, wherein the agent contains an effective dose of the degradation inhibitory agent according to claim 43.

86. A method for identifying a compound that inhibits the degradation of a transcription factor of a glucose metabolism-related gene by calpain, wherein the method comprises contacting calpain and/or the transcription factor with a test compound under conditions that allow the cleavage of the transcription factor by calpain; and determining whether the test compound inhibits the cleavage of the transcription factor by calpain, by introducing a system using a signal and/or a marker capable of detecting the degradation of the transcription factor by calpain and detecting the presence, absence or change of the signal and/or the marker.

87. A method for identifying a compound that inhibits the degradation of a transcription factor of a glucose metabolism-related gene by calpain, wherein the method comprises contacting calpain and/or the transcription factor with a test compound under conditions that allow the cleavage of the transcription factor by calpain; and determining whether the test compound inhibits the

cleavage of the transcription factor by calpain, by introducing a system using a signal and/or a marker capable of detecting the amount of the transcription factor or the amount of a degradation product of the transcription factor and detecting the presence, absence or change of the signal and/or the marker.

88. A method for identifying a compound that inhibits the degradation of a transcription factor of a glucose metabolism-related gene by calpain, wherein the method comprises contacting calpain and/or the transcription factor with a test compound under conditions that allow the binding of calpain to the transcription factor; and determining whether the test compound inhibits the binding of calpain to the transcription factor, by introducing a system using a signal and/or a marker capable of detecting the binding of calpain to the transcription factor and detecting the presence, absence or change of the signal and/or the marker.

89. The identification method according to any one of claims 86 to 88, wherein calpain is m-calpain or  $\mu$ -calpain.

90. The identification method according to any one of claims 86 to 89, wherein the transcription factor of a glucose metabolism-related gene is at least one member selected from the group consisting of hepatocyte nuclear factor 4 $\alpha$ , hepatocyte nuclear factor 1 $\alpha$  and insulin promoter factor 1.

91. A compound identified by the identification method according to any one of claims 86 to 90.

92. A reagent kit containing at least one member selected from the group consisting of calpain, a polynucleotide encoding calpain, and a vector containing a polynucleotide encoding calpain; and at least one member selected from the group consisting of a transcription factor of a glucose metabolism-related gene that is degraded by calpain, a polynucleotide encoding the transcription factor, and a vector containing the polynucleotide.

93. A reagent kit containing at least one member selected from the group consisting of calpain, a polynucleotide encoding calpain, and a vector containing a polynucleotide encoding calpain; and at least one member selected from the group consisting of hepatocyte nuclear factor 4 $\alpha$ , hepatocyte nuclear factor 1 $\alpha$ , insulin promoter factor 1, a polynucleotide encoding any of these,

and a vector containing the polynucleotide.

94. The reagent kit according to claim 92 or 93, wherein calpain is m-calpain or  $\mu$ -calpain.